UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,436	09/06/2005	Silvio Aime	57708/380	7608

35743 7590 01/02/2008

KRAMER LEVIN NAFTALIS & FRANKEL LLP
INTELLECTUAL PROPERTY DEPARTMENT
1177 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	**PAPER NUMBER**
1618	

NOTIFICATION DATE	DELIVERY MODE
01/02/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

klpatent@kramerlevin.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,436	AIME ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	/

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 8/20/2007, in reply to the Office Action mailed 4/18/2007, is acknowledged and has been entered. The Supplemental Response, filed 10/16/2007, is also acknowledged and has been entered. Claims 1 – 13 have been amended per the 8/20/07 filing, and new claims 14 and 15 have been added. Claims 1, 14 and 15 have been further amended per the 10/16/07 filing. Claims 1 – 15 are pending.

Restriction

Newly submitted claims 14 and 15 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly added claims require additional limitations and/or method steps which were not required for the search of the originally presented invention.

The method of claim 14, which is a method for the localization of athersclerotic plaques is a distinct method to the method of claims 1 – 13, a method for cellular labeling, which does not require atherosclerotic plaques. The method of claim 15, which is a method for the detection of occured transfection in gene therapy, is also distinct from the method of claims 1 – 13, which does not require gene therapy. The inventions of claims 1 – 13 (hereinafter Group I), claim 14 (hereinafter Group II), and claim 15 (hereinafter Group III) unrelated. Inventions are unrelated if it can be shown

that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions can have different modes of operation. For example, the method of cellular labeling of Group I, can be practiced either in vitro or in vivo, while the methods of Groups II or III, requiring atherosclerotic plaques or gene therapy, respectively, appear to be directed toward in vivo methods where atherosclerotic plaques are present or gene therapy has been performed.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 14 and 15 are withdrawn from consideration at this time as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Status of claims

Claims 1 – 15 are pending, of which claims 14 and 15 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1 – 13 are readable upon the originally presented invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments, see page 6 of the Response filed 10/16/07, with respect to the objection to the specification have been fully considered. The objection has been WITHDRAWN in view of the amendment filed 8/20/07.

Applicant's arguments, see pages 6 – 8 of the Response filed 10/16/07, with respect to the rejection of claims 1, 4, 6 and 8 – 10 under 35 USC 102(b) as being anticipated by Tokumitsu; the rejection of claims 1, 4 - 7 and 9 - 13 under 35 USC 102(b) as being anticipated by Ranney, and the rejection of claims 1-3 and 6 under 35 USC 102(b) as being anticipated by Kabalka have been fully considered. The rejections have been WITHDRAWN as being overcome by amendment.

New Grounds for Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4 – 7 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Klaveness *et al.* (US 4,985,233), as evidenced by Encylopedia Britannica Article, "Reticuloendothelial System".

Klaveness discloses methods of diagnosis comprising administering to a human body or to a selected region thereof a contrast effective amount of a diagnostic agent comprising a physiologically tolerable, water insoluble, water-swellable, hydroxyl group containing, particulate macromolecular product which is cross-linked to form a three-dimensional network and carries within cavities therein at least one non-radioactive paramagnetic metal species, said product comprising at least one water-insoluble material selected from the group consisting of polysaccharides, polymerized sugar alcohols and derivatives thereof; and generating an NMR or ultrasound image of said region (see claim 1). The paramagnetic metal may be gadolinium or manganese (claim 7). Suitable materials which may be crosslinked to water-insoluble but water-swellable gel particles include dextran (column 4, lines 49 – 54). As an alternative to the paramagnetic species being present within cavities within the macromolecular product (i.e. non-covalently bound), the paramagnetic species can be chemically bound in the macromolecular product via a chelate complex (column 6, lines 1 – 25). Such chelate-forming groups (such as DTPA, EDTA, etc.) are covalently bound to the hydroxyl groups of the polymeric polymerized carbohydrate via a carboxylic acid such as to produce an ester bond to the macromolecular product (column 6, lines 65 - column 7, line 17). When particles consisting of such macromolecular products are degraded in the body, smaller water-soluble fragments are formed. For example,

degradable particles may be taken up by the reticuloendothelial system (RES) of e.g. the liver after parenteral administration for investigation of the liver (column 2, lines 35 – 50).

Normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to: (A) Prove the primary reference contains an "enabled disclosure;" (B) Explain the meaning of a term used in the primary reference; or (C) Show that a characteristic not disclosed in the reference is inherent. For example, "to serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). See MPEP 2131.01.

In the instant case, the Encylopedia Britannica article entitled "Reticuloendothelial System" is included to demonstrate that Klaveness's teaching that the degradable particles are taken up by the reticuloendothelial system for liver investigation inherently meets the limitation that the particles are internalized by cells, as claimed, because the article teaches that the reticuloendothelial system is a class of phagocytic cells that take up particular substances.

Klaveness meets the instant claim limitations of a) exposing insoluble particles comprising a gadolinium chelate bound to a macromolecular component and b)

internalizing the particles inside the cells (i.e. via entrapment by the endothelial system). Upon introduction into the cells, the particles would inherently be exposed to enzymes or effectors in the environment to thereby degrade the particles, as Klaveness also teaches that the particles are degradable. Since Klaveness performs of all of the active claim steps recited, Klaveness accomplishes the claimed method.

Claims 1 and 4, 6 and 8 – 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Shikata *et al.* (*Eur. J. Pharmaceutics and Biopharmaceutics*, 2002, 53, p. 57 – 63).

Shikata discloses the accumulation of gadolinium loaded as gadopentetic acid (Gd-DTPA) in chitosan nanoparticles (Gd-nanoCPs) which was evaluated in vitro in cultured cells (abstract). The Gd-nanoCPs were designed for gadolinium capture therapy for cancer, which can be integrated with MRI diagnosis (page 57, left column). Shikata meets the instant claim limitations of a) exposing insoluble particles comprising a gadolinium chelate entrapped in a chitosan network to cells and b) internalizing the particles inside the cells. Upon introduction into the cells, the particles would inherently be exposed to enzymes or effectors in the environment to thereby degrade the particles, as Shikata also teaches that chitosan is biodegradable (bioerodible) (page 57, right column). Since Shikata performs of all of the active claim steps recited, Shikata accomplishes the claimed method.

Claims 1 - 3 and 6 are rejected under 35 U.S.C. 102(a) as being anticipated by Kabalka *et al.* (*Mag. Res. in Medicine*, 1988, 8, 53, p. 89 – 95), as evidenced by Encylopedia Britannica Article, "Reticuloendothelial System".

Kabalka discloses gadolinium-labeled liposomes as paramagnetic contrast agents. An amphipathic derivative of the chelating ligand diethylenetriaminepentaacetic acid is prepared (i.e. DTPA-SE), by conjugation of stearyl alcohol to DTPA via an ester bond (see Figure 1, page 90). Liposomes were formed mixing Gd-DTPA, egg phosphatidylcholine, and cholesterol, and were then dried, vacuum desiccated and resuspended in phosphate buffered saline. The suspensions were sonicated to produce the desired small unilamellar vessicles with an average diameter of 0.05 micrometer (page 91). The liposomes can be used to deliver antibiotics, chemotherapeutic agents, or Gd-DTPA to the liver because they are rapidly entrapped by the endothelial system and concentrate in normal liver (page 89 and 92). The liposomes containing paramagnetic amphiphilic agents significantly enhance the MR signal intensity in T1-weighted MRI, and appear to be suitable contrast agents for enhancement of organs such as the liver, spleen, bone marrow, and other organs rich in macrophage (i.e. phagocytotic cells) activity.

Normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to: (A) Prove the primary reference contains an "enabled disclosure;" (B) Explain the meaning of a term used in the primary reference; or (C) Show that a characteristic not disclosed in the reference is inherent.

For example, "to serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). See MPEP 2131.01.

In the instant case, the Encylopedia Britannica article entitled "Reticuloendothelial System" is included to demonstrate that Kabalka's teaching that the liposomes are taken up by the reticuloendothelial system inherently meets the limitation that the particles are internalized by cells, as claimed, because the article teaches that the reticuloendothelial system is a class of phagocytic cells that take up particular substances.

Kabalka meets the instant claim limitations of a) exposing insoluble particles comprising a gadolinium chelate having an aliphatic chain conjugated thereto and b) internalizing the particles inside the cells (i.e. via entrapment by the endothelial system). Upon introduction into the cells, the particles would inherently be exposed to enzymes or effectors in the environment to thereby degrade the particles, as Kabalka also teaches that the gadolinium-labeled liposomes containing the diester reagent are cleared from the liver rapidly as a consequence of the labile nature of the ester linkages in the acidic environment of the liver (page 94). Since Kabalka performs of all of the active claim steps recited, Kabalka accomplishes the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2 and 4 – 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness *et al.* (US 4,985,233), in view of Grinstaff *et al.* (US 5,498,421).

Klaveness teaches degradable water-insoluble macromolecular particles containing a paramagnetic species and methods of use thereof, as set forth above

Klaveness does not specifically teach a targeting moiety on the particles, and does not teach that chitosan is the polysaccharide which is employed.

Grinstaff teaches compositions useful for the in vivo delivery of biologic which is associated with a polymeric shell formulated from a biocompatible material (abstract). Suitable biologics to be encompassed within the shell include paramagntic cations such as Gd, Mn, etc. (column 7, lines 10 – 15 or column 14, line 32). The polymeric shells

can be administered intravenously, making imaging of vascularized organs possible. Organ specificity is achieved as a result of uptake of micron-sized organofluorine-containing polymeric shells by the reticuloendothelial system (RES). In addition, lymph nodes within the lymphatic circulation contain cells of the RES (column 6, lines 58+). The polymeric shells containing solid, liquid of gas cores of biologic allows for delivery, and the walls of the polymeric shell are generally completely degradable in vivo by proteolytic enzymes (column 15, line 15 – 23). Suitable polymeric shells include polysaccharides (e.g. cellulose, dextrans, alginates, chitosan, and the like) (column 8, lines 49 – 51). Other functional proteins, such as antibodies, which facilitate targeting of a biologic to a desired site can also be used in the formulation of the polymeric shell (column 9, lines 10 – 13).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to include a targeting moiety on the particles disclosed by Klaveness because it is well-known in the art to include such substances on similar polymeric particles for the purposes of site-directed imaging or delivery, as taught by Grinstaff. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because such targeting moieties offer benefits such as site-specific imaging. It would have been further obvious to substitute chitosan as a functionally equivalent saccharide polymer to those employed by Klaveness, and one would have had a reasonable expectation of success in doing so, because Grinstaff teaches that chitosan is analogous to those employed by Klaveness for preparing polymeric particles. Both Klaveness teach and Grinstaff teach degradable polymeric

particles having paramagnetic species encompassed therein which may be taken up by the reticuloendothelial system (RES) of e.g. the liver after parenteral administration for investigation and imaging of the liver, thus the claimed method of cellular uptake and particle degradation would be accomplished upon administration of the modified particles.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

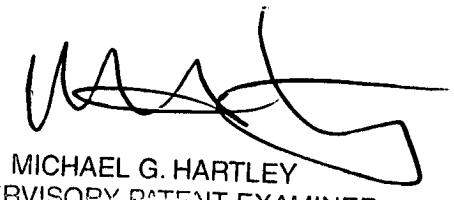
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS



MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER